Delayed Diagnosis of Kawasaki Syndrome: An Analysis of the Problem

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Delayed Diagnosis of Kawasaki Syndrome: An Analysis of the Problem

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ABSTRACT. *Objective.* **Most pediatric providers in Colorado are familiar with Kawasaki syndrome (KS). However, in a recent outbreak, 30% of cases were diagnosed after illness day 10. We hypothesized that these children saw providers who were not familiar with KS, were given antibiotics for other diagnoses that delayed identification, had access-to-care issues, or presented atypically.**

Methods. **A retrospective chart review of 106 consecutive KS cases seen at the Children's Hospital in Denver during 1994–2000 was conducted.**

Results. **Twenty-five of 106 children (23.6%) were diagnosed after day 10 of illness (delayed-diagnosis group [DDG]), and these 25 cases were compared with 81 cases diagnosed on or before day 10 (early-diagnosis group [EDG]). There were no differences between patients in the DDG and EDG in age, gender, number of visits, specialty of the primary care physician, time to the first medical visit, number of antibiotics received, coronary artery abnormalities, white blood cell count, or erythrocyte sedimentation rate. Patients in the DDG had significantly more days of fever, rash, red eyes, and oral changes. A platelet count of >450 000/mm^3 occurred more often in the DDG (56%) than the EDG (30%). After additional analysis, patients in the EDG had close clustering of symptom onset in the first few days of illness, but patients in the DDG had onset of symptoms scattered over 9 days. Patients in the DDG were 2.8 times more likely to have coronary artery aneurysms than patients in the EDG (DDG: 24%; EDG: 8.6%).**

Conclusions. **Diagnosis after the 10th day of illness was not linked to type of medical provider, number of antibiotics received, or number of physician visits. Patients in the DDG exhibited the typical features of KS, but the onset of their symptoms was dispersed over time as opposed to the close clustering of symptoms in the EDG. Because coronary artery aneurysms occurred significantly more often in the patients in the DDG, more education is needed to teach health care providers to have a high index of suspicion for KS in young children presenting with fever/rash illnesses.** *Pediatrics* **2005; 115:e428–e433. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1824;** ***Kawasaki syndrome, coronary artery aneurysms, delayed diagnosis.***

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ABBREVIATIONS. KS, Kawasaki syndrome; IVIG, intravenous immunoglobulin; DDG, delayed-diagnosis group; EDG, early-diagnosis group; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NS, not significant.

Kawasaki syndrome (KS) is an acute, vasculitic illness of young children that typically presents with fever, bilateral nonexudative conjunctivitis, mucous-membrane changes, swollen extremities, and/or palm and sole erythema, rash, and adenopathy.[1–3] The etiology of this serious disease remains unknown, and there is no laboratory test to identify affected children reliably. Diagnosis of this disease is made by recognition of clinical signs consistent with the KS diagnostic criteria and excluding other diseases.[4]

Treatment with high-dose intravenous immunoglobulin (IVIG) in combination with aspirin before the 10th day of illness significantly decreases the risk of coronary artery abnormalities.[5,6] The efficacy of treating patients with KS by using IVIG after 10 days of illness is unknown; therefore, early diagnosis and treatment is desired. Data collected during a previous study of patients with KS in Colorado revealed that 30% of patients hospitalized for treatment of KS at the Children's Hospital in Denver were diagnosed after day 10 of illness.[7,8] We hypothesized that these children might see nonpediatricians, be given antibiotics for other diagnoses that delay identification, be brought to medical attention late because of a variety of access-to-care issues, or present atypically. Identification of the characteristics of those children who are diagnosed late might be helpful in promoting earlier recognition.

METHODS

After approval by the Colorado Multi-institutional Review Board, a retrospective chart review of patients' medical records was conducted on all children with the diagnosis of KS admitted to the Children's Hospital during 1994–2000. Charts were identified by discharge diagnosis (*International Classification of Diseases, Ninth Revision* [ICD-9] code 446.1), and each chart was examined by 1 of the co-investigators to ensure that they met clinical criteria for KS as recognized by the current American Heart Association diagnostic guidelines.[4] A Kawasaki intake form, routinely filled out on all patients with KS by an infectious-disease physician, contained detailed information about onset of symptoms, visits to physicians before hospitalization, and medication use. In addition, medical records from the primary care physician (for visits related to the illness prompting admission) were sought at the time of consultation and thus were available in the patients' medical records. Information extracted from the medical record included demographic data, primary care provider's specialty (pediatrics, family medicine, etc), antibiotics prescribed (type and duration), clinical symptoms, laboratory results, echocardiogram results, number of visits from onset of symptoms to diagnosis, and num-

ber of days from onset of symptoms to diagnosis. The presence or absence of coronary artery abnormalities (aneurysms, dilation, or ectasia), and specifically coronary artery aneurysms, was recorded for all patients. Coronary artery abnormalities (including aneurysms) were documented as present if they were seen on any echocardiogram at either presentation or follow-up. A patient in the delayed-diagnosis group (DDG) was defined as a child diagnosed with KS >10 days from the onset of fever. A patient in the early-diagnosis group (EDG) was defined as a child diagnosed with KS ≤10 days from fever onset. The first day of fever was defined as illness day 1. Characteristics of the patients in the EDG and DDG were compared.

Statistical analysis included use of the χ^2 or *t* test for comparisons between the 2 groups. Data from groups that were not normally distributed were compared by using the Mann-Whitney *U* test. Pearson correlation coefficients were calculated to establish correlations between demographic data, clinical manifestations, and laboratory results with the diagnosis of KS. Factors that were identified by Pearson correlation coefficients as being significantly linked were used as variables in a logistic regression model. In this model "$\log_{10}$ days of illness" was used as the dependent variable, and logistic regression used to identify the strongest predictors for early diagnosis of KS.

RESULTS

Patient Characteristics

One hundred nine charts were identified with a discharge diagnosis of KS. Three charts were excluded from analysis because the patients were subsequently given an alternative diagnosis. A total of 106 charts were analyzed. Twenty-five of 106 patients (23.6%) were diagnosed with KS after illness day 10 (DDG), and 81 (76.4%) were diagnosed before the 10th day of illness (EDG). The age, gender, and race/ethnicity distribution of our patients is shown in Table 1, and no significant differences were noted between the 2 groups. Laboratory features and potential risk factors for delayed diagnosis of KS are listed in Table 2. Total number of days of fever, rash, red eyes, oral changes, and extremity changes were significantly greater in the DDG. There was no significant difference in primary residence (inside or outside of metropolitan Denver), primary care provider type (family practitioner versus pediatrician), number of antibiotics prescriptions given, day of illness the patient first visited a medical provider, or the number of visits to a health professional before admission. The C-reactive protein (CRP) count at admission was significantly higher in the EDG than DDG (12.5 vs 5.7 mg/dL). In contrast, erythrocyte sedimentation rate (ESR) on admission was not significantly different. Platelet counts of >450 000/mm^3 were found significantly more often in the patients in the DDG.

To try to define which significant univariate variables best predicted the time until diagnosis of KS, a stepwise linear-regression model was used. Using $\log_{10}$ days of illness before diagnosis as the dependant variable, the significant predicting variables were days of fever, days of rash, and platelet count ($R^2 = 0.75$; $P < .001$).

Physician Visits

Many children in both the EDG and DDG were noted to have seen a health care professional at least 4 times before diagnosis and admission (Fig 1): 44% of the patients in the DDG had ≥4 visits vs 34% of those in the EDG (P = not significant [NS]). The vast majority of patients (95.1%) saw a medical provider at least once during their first 5 days of illness (Fig 2). Fifty-six percent of patients with KS first presented to a medical provider on day 1 or 2 of illness. Only 5 of 106 children were given the diagnosis of KS at the first visit. Initial diagnoses of all patients are listed in Table 3. Streptococcal pharyngitis, otitis media, or viral syndrome were the most common initial diagnoses in both the EDG and LDG.

Hospitalization

At the time of hospitalization, 85 of 106 patients had an admitting diagnosis of KS. Twenty-one patients (Table 4) had another admitting diagnosis but ultimately were determined to have KS. Patients in the DDG were significantly more likely to be diagnosed after hospital admission. For 11 of 81 patients in the EDG and 10 of 25 in the DDG, the diagnosis of KS was made after admission ($P < .01$).

Coronary Artery Abnormalities

Twenty patients with KS had coronary artery abnormalities recognized at the time of diagnosis and before IVIG administration. Three additional patients had a normal echocardiogram at diagnosis, but coronary artery abnormalities were noted on subse-

TABLE 1. Demographic Characteristics of Patients With KS

	EDG, *N* (%)	DDG, *N* (%)	*P* Value	Total, *N* (%)
Age, y				
<1	13 (16)	6 (24)	NS	19 (17.9)
1 to <5	52 (64.2)	12 (48)	NS	64 (60.3)
5 to <12	16 (19.8)	7 (28)	NS	23 (21.8)
Total	81 (100)	25 (100)		106 (100)
Gender				
Female	22 (27.2)	5 (20)	NS	27 (25.5)
Male	59 (72.8)	20 (80)	NS	79 (74.5)
Total	81 (100)	25 (100)		106 (100)
Ethnicity/race				
White, not Hispanic	45 (55.6)	15 (60)	NS	60 (56.6)
Hispanic	14 (17.3)	3 (12)	NS	17 (16.0)
Black	8 (9.8)	2 (12)	NS	11 (10.4)
Asian/Pacific Islander	6 (7.4)	1 (4)	NS	7 (6.6)
Unknown	8 (9.8)	3 (12)	NS	11 (10.4)
Total	81 (100)	25 (100)		106 (100)

TABLE 2. Laboratory Features and Potential Risk Factors of Delayed Diagnosis in KS

Characteristic	EDG	DDG	*P* Value
Days of fever, mean (95% CI)*	6.1 (5.6–6.7)	13.0 (12.0–14.0)	<.005
Days of rash, mean (95% CI)*	4.1 (3.4–4.7)	10.1 (8.9–11.4)	<.005
Days of red eyes, mean (95% CI)	5.2 (4.1–6.2)	7.0 (5.2–8.9)	.005
Days of oral changes, mean (95% CI)	2.7 (2.0–3.8)	6.3 (4.8–7.8)	.02
Days of extremity changes, mean (95% CI)	1.5 (0.8–2.1)	3.8 (2.7–4.9)	.001
Presence of adenopathy, %	39.3	12.0	.01
CRP, mg/dL, mean (95% CI)	12.5 (10.5–14.7)	5.7 (1.97–9.4)	.002
Platelet count >450 000/mm^3, %*	30.0	56.0	.018
ESR, mm/h	65.4 (59.4–71.4)	56.7 (45.8–67.5)	NS
Age, y, mean (95% CI)	2.9 (2.3–3.4)	3.3 (2.5–4.5)	NS
Residence in metropolitan Denver, %	64.5	69.0	NS
Type of primary care provider, % pediatricians	83	75	NS
No. of antibiotic prescriptions, mean (95% CI)	1.7 (1.5–2.0)	2.1 (1.6–2.6)	NS
First contact with medical provider, day of illness, mean (95% CI)	2.7 (2.3–3.0)	2.5 (1.8–3.1)	NS
Number of medical providers seen before diagnosis, mean (95% CI)	3.11 (2.9–3.3)	3.4 (3.0–3.8)	NS

* In a stepwise linear-regression model, using $\log_{10}$ days of illness prior to diagnosis as the dependant variable, the significant predicting variables to diagnosis were days of fever, days of rash, and platelet count ($R^2 = 0.75$; $P < .001$).

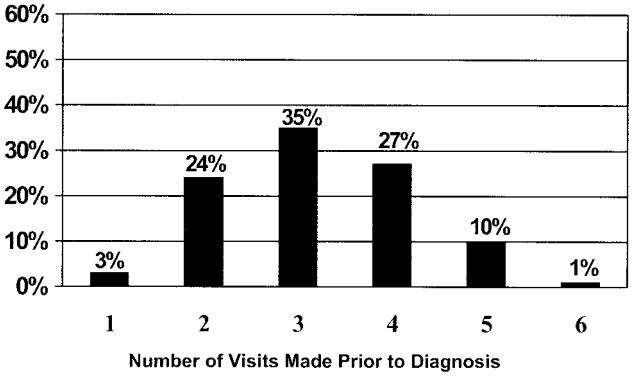

Fig 1. Number of visits to health care providers made by patients with KS before diagnosis.

quent echocardiograms despite IVIG therapy. These 3 patients were diagnosed and treated with IVIG on illness days 8, 3, and 3. Although there was a trend for patients in the DDG to have more coronary artery abnormalities than those in the EDG (28% vs 18.5%, respectively), this difference was not statistically significant (Table 5). Children with KS that were <1 year old were 2.9 times more likely to develop coronary artery abnormalities (47.4% vs 16%; $P < .01$) and 5.3 times more likely to develop aneurysms (36.8% vs 6.9%; $P < .01$) than children >1 year old. Patients in the DDG were 2.8 times more likely to have coronary artery aneurysms than those in the EDG (24% vs 8.6%; $P = .04$).

Time to Appearance of Physical Signs of KS

In an effort to better understand and analyze the EDG and DDG, we developed a timeline of the presentation of the signs of KS for each group. The mean day of onset of each sign relative to the first day of fever is noted (Fig 3). Patients in the EDG and DDG are shown separately. The time from onset of illness until first contact with a medical provider was similar for the EDG (2.7 days) and the DDG (2.5 days; *P* = NS). The development of additional KS signs was tightly clustered in the EDG and appeared before the sixth day of illness. In contrast, patients in the DDG had the onset of additional signs dispersed over 9 days. Patients in the DDG presented later for a second medical visit (mean illness day: 6.7; 95% confidence interval [CI]: 5.7, 7.8 days) than patients in the EDG (mean illness day: 4.6; 95% CI: 4.0, 5.1 days; $P = .001$).

DISCUSSION

Health care providers in Colorado have had considerable experience with KS. There have been 3 outbreaks in Colorado investigated by the Centers for Disease Control and Prevention in the last 20 years, and physicians throughout the state have aided in these investigations.[3,8,9] The Children's Hospital (Denver) is a large tertiary care pediatric hospital, and our infectious-disease group routinely takes calls from providers throughout the state for questions and referrals related to KS. Questions regarding KS are one of our most common telephone inquiries, indicating that KS is often considered in the differential diagnosis of febrile children. Our infectious-disease group requests that patients with possible KS be referred to our center for diagnosis and treatment. Therefore, we were concerned by the fact that 23.6% of children with KS were diagnosed after day 10 of illness.

Late diagnosis is problematic because patients in the DDG were more likely to develop coronary artery aneurysms than those in the EDG (24% vs 8.6%, respectively; $P = .04$). Patients in the DDG may have prolonged untreated inflammation that puts them at higher risk for aneurysms, which is substantiated by the continued elevation of the ESR (mean: 56.7 mm/hour) and CRP (mean: 5.7 mg/dL) seen at diagnosis in these children.

There were a number of initial hypotheses that we believed would explain why so many patients with KS were diagnosed after day 10, including (1) medical specialty of the provider (pediatricians are more likely to be trained to recognize the disease than nonpediatricians), (2) patients in the DDG given antibiotics for other diagnoses, which delayed identifi-

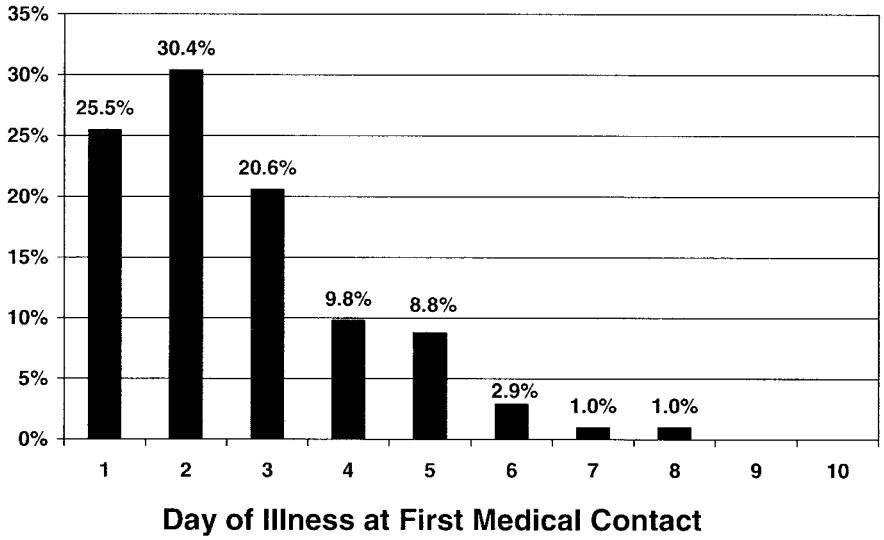

Fig 2. Day of illness when patients with KS first sought medical attention.

TABLE 3. Patient Diagnoses at First Medical Visit

Diagnosis	Cases, *n* (%)
Streptococcal pharyngitis	28 (26.4)
Otitis media	22 (20.8)
Viral syndrome	20 (18.9)
KS	5 (4.6)
Adenitis	5 (4.6)
Rule out serious bacterial infection	5 (4.6)
Urethral meatitis	1 (1)
Urinary tract infection	3 (2.8)
Pneumonia	2 (1.9)
Scarlet fever	1 (1)
Abdominal pain	1 (1)
Oral candidiasis	1 (1)
Hepatitis	1 (1)
Sinusitis	1 (1)
Candidal diaper rash	1 (1)
Unknown/left blank	4 (3.8)
Records of initial visit not obtained	5 (4.6)
Total	106 (100)

TABLE 4. Initial Admitting Diagnosis in the 21 Patients With KS in Whom the Diagnoses Were Made After Hospitalization

Admitting Diagnosis	No. of Patients
Adenitis	2
Fever of unknown origin	5
Meningitis	1
Myocarditis	1
Osteomyelitis	1
Probable influenza	1
Possible sepsis/bacteremia	3
Possible testicular torsion	1
Pyelonephritis, dehydration	1
Stevens-Johnson syndrome	1
Toxin mediated disease	3
Viral sepsis	1
Total	21

cation, (3) access-to-care problems (patients in the DDG were initially brought to medical attention later), or (4) milder disease or atypical presentation in the DDG. All these hypotheses were largely refuted by the study data.

The medical specialty of the primary care doctor (family medicine versus pediatrics) was not a significant factor in whether the patient was in the EDG or DDG. The data did not support our hypothesis that pediatricians may see more cases of this disease in both training and practice and therefore recognize this diagnosis earlier. Also, the mean number of prescriptions for antibiotics was not significantly different in the EDG versus DDG.

A large number of patients (44% DDG vs 34% EDG) saw a medical provider at least 4 times before diagnosis (P = NS). This observation argues against significant barriers in accessing care. Ninety-five percent of patients with KS presented to a provider in the first 5 days of illness, yet the mean illness day at diagnosis was 8.5 days. Five children were diagnosed with KS at the first medical visit. A number of alternative initial diagnoses were given to the other 101 children. Most of the diagnoses reflect recognition of at least some of the signs and symptoms associated with KS. For example, the diagnosis of urinary tract infection reflects recognition of pyuria. Patients in both the EDG and DDG had an average of 3 visits to medical providers before the diagnosis of KS. These data highlight the missed opportunities to make a diagnosis of KS earlier in some of these patients. There are multiple other descriptions in the literature of patients ultimately diagnosed with KS who were initially given the diagnosis of other entities such as cervical adenitis,[10–12] meningitis,[13,14] pneumonia,[15] appendicitis,[16,17] or pyelonephritis.[18] It is interesting to note that in this study, the children in the DDG were overrepresented in the group of children hospitalized before the diagnosis of KS, which suggests that either children in the DDG presented incompletely[19] or the provider was focused on only 1 sign or aspect of illness (ie, adenopathy for admitting diagnosis of adenitis).

Although 1 of our initial hypotheses was formulated on the assumption that patients in the DDG might have clinical and/or laboratory manifestations that differ substantially from those in the EDG, this was generally not demonstrated by this study (Table 2). Patients in both the EDG and DDG largely manifested "typical" KS signs and symptoms: fever, nonexudative conjunctivitis, red/cracked lips, rash, and swollen hands and feet. The 2 groups generally did

TABLE 5. Coronary Artery Findings of Patients With KS According to Time of Diagnosis

Characteristic	EDG	DDG	*P* Value	Relative Risk
Coronary artery abnormalities*	16/81 (18.5%)	7/25 (28%)	NS	1.4
Coronary artery aneurysms†	7/81 (8.6%)	6/25 (24%)	.04	2.8

* Coronary artery abnormalities are dilation, ectasia, or aneurysms observed on initial or follow-up echocardiogram.
† Coronary artery aneurysms are aneurysms observed on initial or follow-up echocardiogram.

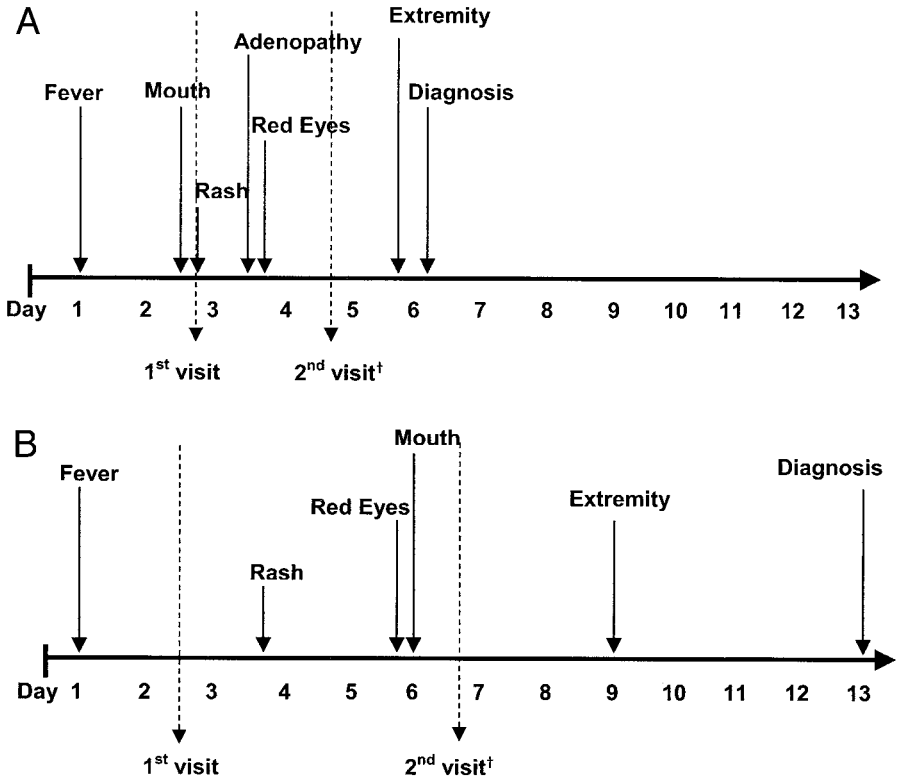

Fig 3. Appearance of signs in patients with KS. A, EDG. Note the tight clustering of KS signs in the first 5 days of illness. B, DDG. Note the onset of signs developing over 9 days (adenopathy was seen in only 3 of 25 in the DDG at days 1, 5, and 9). †, mean time from illness onset to second visit was 4.6 days EDG versus 6.7 days DDG ($P = .001$).

not differ in the types of signs and symptoms, but they did differ in the timetable of onset of those signs (Fig 3). The logistic-regression analysis found number of days of fever, rash, and platelet count of $>450\,000/mm^3$ to be the strongest predictors of the diagnosis of KS. If patients in the DDG had presented "atypically" or "incompletely,"[19] we might expect that at least 1 of the variables of fever, rash, and/or platelet count would not be included as strong predictors of KS in these children. The strong association of these features with the diagnosis of KS (logistic regression) and the timetable of onset of KS signs (Fig 3) suggest that patients in the DDG demonstrated the usual features of KS, albeit over a prolonged course of time.

We developed the model depicted in Fig 3 in an effort to further understand the time line of onset of KS signs and its potential relevance to delayed diagnosis. We postulate that the close clustering of symptoms in the EDG prompted parents to return earlier to medical attention and for physicians to recognize the cluster and consider the diagnosis of KS. This model strongly suggests that delay in development of the usual symptoms of KS in a subgroup of patients may be a factor in late diagnosis.

Most patients in the EDG presented at their first visit with both fever and mouth changes, and ~50% had rash present as well. The combination of these signs might have prompted physicians to be more suspicious of KS or to advise parents to return for persistent fever or onset of other KS signs. In contrast, most patients in the DDG had only fever at their first visit. Therefore, until the onset of extremity changes on day of illness 9 (mean), the clinical criteria would not have been satisfied in 22 of the 25 patients in the DDG (only 3 of 25 patients in the DDG had a history of adenopathy). This may partially account for the delayed diagnoses in these patients. The mean day of the third medical visit for the DDG was on illness day 12.5 (illness day 5.7 for the EDG). This visit closely coincides with the mean day of diagnosis for the DDG (day 13).

Children <1 year old with KS were significantly more likely to develop coronary artery abnormalities or aneurysms than older children. This observation has been noted in other studies.[20–22] The mean age of the EDG and DDG were not different. The proportion of children <1 year old in the EDG and DDG was not significantly different (Table 2); however, there were only 19 of 106 children <1 year old (13 in the EDG and 6 in the DDG). The percentage of males

in both groups is higher than generally reported for patients with KS, and this is of uncertain significance.

There are several possible weaknesses or biases of this study. Data for this study were based on medical-record review. It is possible that parents of patients that were ill the longest (DDG) were less accurate in their recall. However, we were able to confirm the timeline of symptoms and signs and laboratory results in a majority of the patients by reviewing both admission records from our hospital as well as accompanying records from primary care physician visits. It is also possible that cases of KS were miscoded (eg, not identified in our search by *International Classification of Diseases, Ninth Revision* code) and therefore not included for analysis. Finally, because the DDG consisted of only 25 patients, it may not have been large enough to demonstrate a difference when one might exist. For example, when comparing frequency of coronary artery abnormalities, there was a higher percentage of patients in the DDG that developed abnormalities compared with those in the EDG (28% vs 18.5%, respectively; P = NS); it is possible that with more patients, this difference might have been statistically significant.

This study underscores the importance of timely diagnosis of KS and institution of therapy as soon as possible. For a subset of patients, signs and symptoms that constitute the current criteria for the clinical diagnosis of KS may appear over a protracted period of time, making identification more difficult and delaying diagnosis. Patients with KS diagnosed after 10 days (DDG) were more likely to develop coronary artery aneurysms. It is unknown whether the patients in the DDG were inherently predisposed to develop aneurysms or if aneurysms were more likely to develop as a function of more days of ongoing inflammation. A diagnostic test for KS is needed to identify these children earlier. In the meantime, the American Heart Association's Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease is developing an algorithm to help clinicians decide which patients, who do not definitively fulfill diagnostic criteria for KS, may benefit from therapy.

CONCLUSIONS

Twenty-four percent of children in our study were diagnosed with KS after the 10th day of illness. Patients in the DDG exhibited the typical features of KS; however, they had onset of KS signs dispersed over time as opposed to the close clustering of signs seen in the EDG. Patients with KS typically had multiple visits to providers before the diagnosis was made. More education is needed to teach health care providers to recognize the features of KS in febrile children and to have a high index of suspicion for KS in young children presenting with fever/rash illnesses.

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